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EXAMINER	
REDDIG, PETER J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,224	MUELLER-HERMELINK ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed December 31, 2007 in response to the Office Action of July 31, 2007 is acknowledged and has been entered. Previously pending claims 111-133 have been amended. Claims 111-134 are currently being examined.

2. The following rejections are being maintained:

Priority

3. The priority date for claims 111-122 and 124-132 remains July 2, 2003 and the priority date for claims123, 133, and 134 is July 6, 2002.

Applicants argue that submitted herewith are certified English translations of the three German priority applications, namely DE 102 29 906.4, DE 102 29 907.2 and DE 102 30 516.1. Support for the claims, as amended, can be found throughout each of the priority applications. Accordingly, applicants maintain that in view of the submission of the certified English translations, the subject application has a July 4, 2002, priority date.

Applicants arguments have been considered, but support could only be found for monoclonal antibody PM-2, which comprises SEQ ID NO: 5 and 7, an antigen binding fragment thereof, and a cell line producing said antibody in Application DE 102 30 516.1, filed 7/6/2002. Support for the broadly claimed antibodies of claims 111-122 and 124-132 was not found in German priority applications DE 102 29 906.4, DE 102 29 907.2 and DE 102 30 516.1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 111-122 and 124-130 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons previously set forth in section 5, pages 3-4 of the Office Action of July 31, 2007.

Applicants argue that Claims 111 to 130 are clear and definite under 35 U.S.C. §112, second paragraph. In terms of why the antibody binds to polypeptides having different molecular weights, there are a variety of possibilities. In this regard, without being bound by any particular possibility the molecular weight of intact protein could be 110 kDa which, if degraded during preparation or size fractionation by electrophoresis, forms a 55 kDa fragment. Thus, the antibody could bind to both 55 and 110 kDa molecular weight forms if the epitope is present on the intact110 kDa protein and the 55 kDa degradation product. Another possible explanation is that the 110 kDa form represents an unprocessed protein containing the epitope, whereas the 55 kDa form represents a proteolytically processed (cleaved) version of the 110 kDa protein; again the antibody can bind to 55 and 110 kDa molecular weight forms since the epitope is present on both forms. There are other possible explanations, all of which would be known to the skilled artisan. Given that there are several plausible explanations why the antibody binds to different molecular weight proteins, which explanations would be known to the skilled artisan, the claims are not unclear or indefinite due to the recitation of multiple molecular weights.

Applicants argue that in terms of whether denaturing or non-denaturing conditions were used for the molecular weight determination, as is known in the art sodium dodecyl sulfate is a detergent. Thus, in view of the fact that a detergent was used for size fractionation, the skilled artisan would know that the molecular weight determination was under denaturing conditions.

Given that the skilled artisan would know that denaturing conditions were used for molecular weight determination, the claims are clear and definite.

Applicant's arguments have been considered, but have not found persuasive. Although there may be many ways the two claimed proteins of distinct molecular weights may be produced that are known in the art and Applicant states that the proteins were identified under denaturing conditions, it is still unclear from the teachings of the specification how the claimed polypeptides are produced and whether or not they are parts of one protein or are two distinct proteins. Thus, it is unclear if the claimed antibody is required to bind to two distinct polypeptides or one protein that is degraded or otherwise modified and the claims are indefinite for the reasons previously set forth.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 111-122 and 124-130 remain rejected under 35 U.S.C. 112, first paragraph the reasons previously set forth in section 7, pages 5-14 of the Office Action of July 31, 2007.

Applicants argue that the Examiner has acknowledged that the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, as discussed at length in the Office Action the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were well understood by the skilled artisan at the time of the invention (see, for example, pages 9-11 of the Office Action). The specification also discloses the role of antibody heavy and light chain variable regions, CDR

and FR regions in antigen binding (page 22, line 6, to page 23, line 2). Consequently, in view of the high level of knowledge and skill in the art with respect to antibody structure and function at the time of the invention clearly the skilled artisan would be apprised of antibody regions that participate in antigen binding.

Applicants' arguments have been considered, but have not been found persuasive. Although antibody structure is well known in the art, the cited references demonstrate that single amino acid changes can unpredictably disrupt the function of an antibody. Thus, given the unpredictability of making the broadly claimed antibody that is functional, one of skill in the art would not believe it more likely than not that the broadly claimed antibody would function as claimed.

Applicants argue that in addition to the high level of knowledge and skill in the art with respect to antibody structure and function, as acknowledged by the Examiner the specification discloses the locations of the CDRs in SEQ ID NOs:5 and 7 (page 7 of the Office Action). In particular, the specification discloses the CDRs in SEQ ID NOs:5 and 7 in Figures 14 and 15 (see, also, pages 5, lines 6-7 and 24-25). Furthermore, in view of the fact that the specification discloses the location of the CDRs in SEQ ID NOs:5 and 7 and that SEQ ID NOs:5 and 7 are human sequences, the skilled artisan would know the location of the FRs in SEQ ID NOs:5 and 7. Applicants argue that in view of the above guidance, the skilled artisan would know the location of CDRs and FRs OF SEQ ID NO: 5 and 7.

Applicants' arguments have been considered, but have not been found persuasive. Although the skilled artisan would know the location of CDRs and FRs OF SEQ ID NO: 5 and 7, one of skill in the art would not predictably be able to make all of the claimed variants for the

reasons previously set forth previously and above given the unpredictability of sequence changes on the binding activity of the antibody.

Applicants argue that because the knowledge and skill in the art at the time of the invention was high in terms of antibody structure and function and the location of sequences in SEQ ID NOs:5 and 7 that contribute to antigen binding would be known, the skilled artisan would also know residues in SEQ ID NOs'5 and 7 that would be amenable to substitution and therefore, be able to predict with reasonable certainty variants of SEQ ID NOs:5 and 7 that would have at least partial binding activity. As a non-limiting example illustrating this point, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, for example, outside of a CDR or FR region of in SEQ ID NOs:5 and 7 would likely not destroy antigen binding activity. Thus, the skilled artisan could make a conservative substitution of either SEQ ID NOs:5 or 7 outside of a CDR or FR with a reasonable certainty that the substituted sequence would retain at least partial antigen binding activity. Given the large number of amino residues outside of CDR and FR regions, and the number of amino residues outside of antibody variable regions, clearly many variants of SEQ ID NOs:5 and 7 could be readily produced that have at least partial antigen binding activity. As an additional non-limiting example illustrating this point, the skilled artisan would know that given the role of CDRs in antibody binding a large number of non-conservative amino acid substitutions in the CDRs in SEQ ID NOs:5 and 7 would likely reduce or eliminate antigen binding. Thus, the skilled artisan would know not to delete or introduce a large number of non-conservative substitutions into the CDRs in SEQ ID NOs:5 and 7. Consequently, in view of the guidance in the specification and the high level of knowledge and skill in the art regarding antibody structure and function, the skilled artisan would know of

general regions and particular residues that would be more or less amenable to substitution and could therefore predict SEQ ID NOs:5 and 7 variants likely to have at least partial antigen binding activity without actually having to produce such variants and fragments.

Applicants' arguments have been considered, but have not been found persuasive because, contrary to Applicants' arguments, one of skill in the art would not predictably know where to make the broadly claimed changes given the unpredictability in the art previously set forth and the lack of guidance provided in the specification. Although Applicants postulate that many variants could be produced that have binding activity by making conservative substitutions outsider the CDR or FR, Applicants are arguing limitations not found in the claims and even substitutions that are expected to be conservative do not predictably function as expected for the reasons previously set forth. Although one of skill in the art would know that a large number of non-conservative amino acid substitutions in the CDRs in SEQ ID NOs:5 and 7 would likely reduce or eliminate antigen binding, Applicants are arguing limitations not found in the claims and one of skill in the art could not predictably make the broadly claimed antibody.

Applicants argue that in addition to knowing regions and residues of antibodies that would be more or less amenable to substitution or deletion, the level of knowledge and skill in the art regarding producing antibodies and antigen binding fragments thereof was also high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Furthermore, methods of producing antibody fragments *(e.g.,* Fv, Fab, Fab' and F(ab')2) were known in the art and were routine at the time of the invention. Methods of identifying antibody variants and fragments that bind antigen without undue experimentation were also known in the art and are taught by the

specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Applicants argue that in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention regarding producing antibodies and antigen binding fragments, one skilled in the art could make antibodies and antigen binding fragments that specifically bind a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) which comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7 without undue experimentation.

Applicants' arguments have been considered, but have not been found persuasive. Although the methods for preparation of antibodies and intact antigen binding fragments are well known in the art, the specification has not provided sufficient guidance and exemplification to make the broadly claimed antibodies given the unpredictability in the art of identifying the sequences that can be altered without affecting the function of the antibody. Although, one of ordinary skill could screen for the species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that if the skilled artisan wished to produce variants of SEQ ID NOs:5 or 7, producing recombinant proteins was routine in the art at the time of the invention, and the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as discussed above. Analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to identify antibody variants and fragments that bind to the recited cell types, given that 1) producing antibody variants and fragments was routine; and 2) cell binding and proliferation assays were routine at the time of the invention. Consequently, there is no need for the skilled artisan to "predict" in advance variants or fragments that bind to the recited antigen in order to make variants and antigen binding fragments. In view of the foregoing, the skilled artisan could produce antibody variants and antigen binding fragments without knowing *a priori* the effect of particular substitutions or deletions on activity.

Applicants' arguments have been considered, but have not been found persuasive. Although one could screen for hyrbridomas that have the binding activity claimed, these antibodies would not predictably have the sequence identity to SEQ ID NO: 5 or 7 claimed as the polypeptide(s) claimed are large proteins with multiple epitopes. Thus the majority of antibodies that bound to the claimed proteins would bind to distinct epitopes and would have distinct antigen binding regions, and thus would not predictably have a sequence identity to SEQ ID NO: 5 or 7. Thus, although one could screen for hyrbridomas that have the binding activity claimed they would not predictably be the broadly claimed variant antibodies comprising SEQ ID NO: 5 or 7 claimed. Although Applicant argues that one of ordinary skill could screen for the

species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that the number of antibody variants and antigen binding fragments encompassed by the claims are limited as they are required to bind to antigen and therefore do not include inoperative embodiments. The claimed antibodies and fragments are further limited in number because of the high degree of sequence identity, namely at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Thus, the number of antibody variants and fragments encompassed by the claims will necessarily be limited based upon the functional and structural requirements of antibodies, that the antibodies and fragments will have at least partial antigen binding activity, and that the antibodies and fragments will have a sequence at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7.

Applicants' arguments have been considered, but have not been found persuasive because although the antibodies are required to bind to an antigen, one of skill in the art could not predict which of the broadly claimed antibodies will function to bind the claimed antigen for the reasons previously set forth and above.

6. Claims 111-122 and 124-130 remain rejected under 35 U.S.C. 112, first paragraph as lacking and adequate written description for the reasons previously set forth in section 9 and 11, pages 22-34 of the Office Action of July 31, 2007.

Applicants argue that a proper analysis for written description under 35 U.S.C. § 112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had

possession of the claimed invention. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985). To satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." In re Angstadt, 537 F.2d 498, 502-503 (CCPA 1976), Utter v. Hiraga, 845 F.2d 993,998-99 (Fed. Cir. 1988). Thus, a description of every antibody or antigen binding fragment is not required. Furthermore, the Federal Circuit recently held "that (1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, a genus can be adequately described under 35 U.S.C. § 112, first paragraph without specific examples, an actual reduction to practice, or a complete structure of antibodies and functional fragments.

Applicants argue that in view of the guidance in the specification, which discloses antibody variable heavy and light chain sequences (e.g., SEQ ID NOs:5 and 7), and the high level of knowledge and skill in the art regarding structure and function of antibodies and antigen binding fragments the skilled artisan would be apprised of an adequate number of antibodies and antigen binding fragments within the genus of claims 111 to 133. Consequently, claims 111 to 133 are adequately described.

Applicants' arguments have been considered, but have not been found persuasive because although Applicants discloses antibody variable heavy and light chain sequences (e.g., SEQ ID

NOs:5 and 7) which are the variable regions of the light and heavy chains of the monoclonal antibody PM-2, this single description of antibody that functions as claimed does not describe the broadly claimed genus of antibodies or antigen binding fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) which varies significantly in structure from the exemplified antibody.

Applicants argue that as discussed above, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:5 and 7). The specification also teaches the position of the three CDRs in each heavy and light chain variable region sequence, and therefore the position of the flanking regions (FR). In view of the foregoing guidance in the specification, one skilled in the art would know the location of the amino acid sequences that contribute to antigen binding.

Applicants' arguments have been considered, but have not been found persuasive. Although the positions of the CDRs and FRs are known, the single example of PM-2 does not provide written of the broadly claimed genus of variants whose alterations are unknown.

Applicants argue that as also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge regarding antibody structure and function, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of FRs is acknowledged in the Office Action and is taught by the specification. Thus, in view of the high degree of knowledge and skill in the art concerning antibody structure and

function at the time of the invention, when combined with the guidance of the specification of the heavy and light chain variable sequences, SEQ ID NOs:5 and 7, the location of the CDRs and FRs that contribute to antigen binding, the molecular weights of the antigen and the cells types expressing the antigen, and the high degree of sequence identity to SEQ ID NOs:5 or 7, the skilled artisan would know variants of SEQ ID NOs:5 and 7 that would retain at least partial antigen binding activity. As an illustration, the skilled artisan would know that a conservative substitution outside of a CDR or FR of either SEQ ID NOs:5 or 7 would retain at least partial antigen binding activity. Given the number of amino residues outside of the CDR and FR regions, and the large number of amino residues outside of antibody variable regions, clearly the skilled artisan could readily envision a number of antibody variants and antigen binding fragments within the scope of the claims that have at least partial antigen binding activity of SEQ ID NOs:5 and 7. Consequently, the skilled artisan would be apprised of a number of antibodies and antigen binding fragments within the scope of the claims.

Applicants' arguments have been considered, but have not been found persuasive because, contrary to Applicants' arguments, one of skill in the art would not predictably know where to make the broadly claimed changes given the unpredictability in the art previously set forth and the lack of guidance provided in the specification. Although Applicants postulate that many variants could be produced that have binding activity by making conservative substitutions outsider the CDR or FR, Applicants are arguing limitations not found in the claims and even substitutions that are expected to be conservative do not predictably function as expected as previously set forth. Given that specification only discloses the PM-2 that binds as claimed Applicants does not provide an adequate description of the broadly claimed genus of antibodies

antigen binding fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687).

Applicants argue that in terms of a description of the claimed antibodies and antigen binding fragments to distinguish them from other materials, as discussed above the antibodies and antigen binding fragments are described 1) structurally- they have a high percentage of identity (at least 80%) to heavy or light chain variable sequences, SEQ ID NOs:5 and 7; and 2) functionally- they bind to a polypeptide having an approximate molecular weight of 55 or 110 kDa using SDS- PAGE, wherein the polypeptide is expressed by ASPC-1 and BXPC-3 cells. Thus, as the claimed antibodies and antigen binding fragments are described structurally- they have a heavy or light chain sequence with high degree of sequence identity to SEQ ID NOs:5 and 7, and functionally- they bind to an antigen specified by molecular weight and expressed on particular cells, the antibodies and antigen binding fragments are adequately distinguished from other materials.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have only described a single species that functions as claimed thus Applicants have not provided an adequate description of the broadly claimed species for the reasons set forth above and previously.

Applicants argue that in terms of the concern regarding a description of the antigen to which the antibodies bind, as discussed above the antigen is defined in terms of molecular weight. As also discussed above, the antigen to which the claimed antibodies bind is expressed

by the specified cell types. Finally, the antigen is defined based upon its binding to antibody an antibody comprising SEQ ID NOs:5 and 7. Thus, the antigen can be considered described in view of the specified molecular weight, expression on the two specified cell types and the antibody to which the antigen binds. Furthermore, as discussed above the written description requirement may be satisfied without examples or an actual reduction to practice. In view of the fact that 35 U.S.C. §112, first paragraph does not require examples or an actual reduction to practice, clearly the written description requirement can be satisfied without actually isolating or sequencing the antigen to which the claimed antibodies and fragments bind.

Applicants' arguments have been considered, but have not been found persuasive because the description by approximate molecular weight and the cell in which the antigen is expressed is insufficient to describe the antigen. Given the variability in molecular weight determinations this description does not provide enough structural information to show possession of the claimed antigen and one of skill in the art cannot readily recognize the identity of members of the genus. Thus Applicants have not provided an adequate description of the broadly claimed genus.

Applicants argue that moreover, because the written description requirement under 35 U.S.C. § 112, first paragraph may be satisfied without examples or an actual reduction to practice, the written description requirement can be satisfied if the skilled artisan knows of a number of antibody and antigen binding fragment of species within the claimed genus. Here, in view of the high level of knowledge and skill in the art with respect to antibody structure and function and the guidance in the specification as to the locations of CDRs and FRs in SEQ ID NOs:5 and 7 that participate in antigen binding, clearly the skilled artisan would readily envision a number of antibody and antigen binding fragment species within the claimed genus. Again, as

discussed above, there are many amino residues outside of the CDR and/or FR regions, such that the skilled artisan could readily envision a number of antibody variants and antigen binding fragments within the scope of the claims that have at least partial antigen binding activity.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have only described a single species, the PM-2 monoclonal antibody, that functions as claimed, thus Applicants have not provided an adequate description of the broadly claimed species for the reasons set forth above and previously.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 111-122 and 126-132 remain rejected under 35 U.S.C. 102(a) as being anticipated by Brändlein et al. (Human Antibodies, 18 April 2003, 11:107-119, IDS), for the reasons previously set forth in section 12, pages 34-40 of the Office Action of July 31, 2007.

Applicants argue that Brandlein *et al.* (Human Antibodies 11:107 (2002)) was not published prior to July 4 or 6, 2002, the filing dates of the German priority applications. In support of Applicant's position, submitted herewith as Exhibit A is a copy of an email received from Ms. Susan Hendriks, marketing Coordinator at IOS Press, the publisher of the journal Human Antibodies. In the email, Ms. Susan Hendriks states that "Volume 11, number 4 of

Human An[ti]bodies was published on April 18th 2003." Consequently, Brandlein *et al.* (Human Antibodies 11:107 (2002)) is not prior art against claims 111 to 123 and 126 to 134, and Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive. Although Examiner does not dispute the publication date of Brändlein et al., the priority date for claims 111-122 and 126-132 remains July 2, 2003, for the reasons set forth above, and thus Brändlein et al., is prior art under under 35 U.S.C. 102(a).

8. Claims 111-122 and 126-132 remain rejected under 35 U.S.C. 102(b) as being anticipated by Brändlein et al. (Amer. Assoc. Can. Res., March 29, 2002, 43:970, abstract #4803, IDS) as evidenced by Brändlein et al. (Human Antibodies, 18 April 2002, 11:107-119, IDS), for the reasons previously set forth in section 13, pages 40-44 of the Office Action of July 31, 2007.

Applicants argue that Applicants respectfully point out that a reference cited under 35 U.S.C. §102 must have an enabling disclosure. Thus, for this rejection to be proper, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) must enable claims 111 to 123 and 126 to 134. However, these claims have also been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Consequently, the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §112, first paragraph are contradictory and cannot be maintained simultaneously. Applicants therefore respectfully request that the Patent Office withdraw either the rejection under 35 U.S.C. §102(b) or the rejection under 35 U.S.C. §112, first paragraph.

Applicants' arguments have been considered, but have not been found persuasive. The enablement rejection in section 7 of the Office Action of July 31, 2007, was a scope of enablement rejection with the enabled species being the PM-2 monoclonal antibody comprising

SEQ ID NO: 5 and 7. Given that Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention and this species is enabled. Additionally, the enablement rejection in section 6 of the Office Action of July 31, 2007 was with regard to public availability of the cell line. Given that no evidence has been presented that the cell line producing PM-2 was not publicly available and no evidence has been presented that the cells of the prior art are not the same as those of the instant Application, Applicants arguments are not found persuasive.

Applicants argue that Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to teach or suggest antibodies or antigen binding fragments with a sequence at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. In this regard, there is no sequence information for any antibody, let alone antibodies and antigen binding fragments at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fails to teach or suggest the claimed antibodies. Furthermore, as discussed above reference cited under 35 USC 102 must have an enabling disclosure and there is no antibody sequence described nor any method to obtain any antibody described in Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)). Absent antibody sequence or a method to obtain the antibody one skilled in the art could not produce the antibody. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to enable claims 111 to 123 and 126 to 134.

Applicants' arguments have been considered, but have not been found persuasive because Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, thus the PM-2 monoclonal antibody will inherently be the antibody of the instant invention comprising SEQ ID NO: 5 and 7, which is an enabled species for the reasons set forth above. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." Given that the PM-2 antibody of Brändlein et al. appears to be a species of the broadly claimed antibody for the reasons previously set forth, the species in that case will anticipate the broadly claimed genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 124 and 125 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) as applied to claims 111-122 and 126-132 above, and in further view of Taylor (US Patent No. 5,001,225,

December, 8 1986, previously cited), for the reasons previously set forth in section 14, pages 45-47 of the Office Action of July 31, 2007.

Applicants argue that as discussed above, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to describe any antibody sequences, let alone antibodies and antigen binding fragments at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract#4803 (2002)) fail to teach or suggest each and every element of claims 124 and 125.

Applicants argue that without sequence information or a method to produce the antibody, one skilled in the art would not have a had a reasonable expectation of success at the time of the invention of producing an antibody or an antigen binding fragment at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to provide a reasonable expectation of success in producing an antibody or an antigen binding fragment at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7 of claims 124 and 125.

Applicants argue that the secondary reference of Taylor *et al.* (US Patent 5,001,225) fails to provide that which is missing from Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)). In this regard, there is no sequence described in Taylor *et al.* at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) and Taylor *et al.* (US Patent 5,001,225) fail to teach or suggest each and every element of claims 124 and 125.

Applicants argue that in sum, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) alone or in combination with Taylor *et al.* (US Patent 5,001,225) fail to teach or

suggest each and every element of claims 124 and 125, and fail to provide a reasonable expectation of success in producing an antibody or an antigen binding fragment at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7 of claims 124 and 125.

Applicants' argument has been considered, but has not been found persuasive since applicant is arguing and discussing the reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). In particular, the combined references teach the enabled species of the PM-2 monoclonal antibody which will inherently be the antibody of the instant invention comprising SEQ ID NO: 5 and 7, which is an enabled species for the reasons set forth above, and the claimed antibody fragments and detectable agents and motivation for making the combined products.

Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

10. Claims 123, 133, and 134 are rejected under 35 U.S.C. 102(a) as being anticipated by Brändlein et al. (Amer. Assoc. Can. Res., March 29, 2002, 43:970, abstract #4803, IDS) as evidenced by Brändlein et al. (Human Antibodies, 18 April 2002, 11:107-119, IDS) and Appendix 1, for the reasons previously set forth in section 13, pages 40-44 of the Office Action

of July 31, 2007 and for the reasons set forth above. Appendix 1 shows the date of receipt of Brändlein et al. (Amer. Assoc. Can. Res) at the USPTO library as March 29, 2002.

11. All other objections and rejections recited in the Office Action of July 31, 2007are withdrawn.

12. No claims allowed.

13. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice

of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

14. Applicants submission of the translated priority documents prompted the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/

Examiner, Art Unit 1642

/P. J. R./

/Karen A Canella/

Primary Examiner, Art Unit 1643